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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,026	02/14/2006	Zhenping Zhu	11245/48503	7237

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EXAMINER	
HUYNH, PHUONG N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,026	ZHU, ZHENPING	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *One* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-43* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-43 are pending.

REQUIREMENT FOR UNITY OF INVENTION

As provided in 37 CFR 1.475(a), a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in a national stage application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim. See 37 CFR 1.475(e).

When Claims Are Directed to Multiple Categories of Inventions:

As provided in 37 CFR 1.475(b), a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:

(1)A product and a process specially adapted for the manufacture of said product; or

(2)A product and process of use of said product; or

(3)A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or

(4)A process and an apparatus or means specifically designed for carrying out the said process; or

(5)A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.

Otherwise, unity of invention might not be present. See 37 CFR 1.475(c).

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 4-18, 28-29, 31, 32, 34 and 35, drawn to an antibody having a first antigen binding site specific for a first VEGF receptor and a second antigen binding site specific for a second VEGF receptor, wherein the **first receptor is KDR and the second receptor is Flt-1**.

II. Claims 4, 6-17, 28, 31, 34, drawn to an antibody having a first antigen binding site specific for a first VEGF receptor and a second antigen binding site specific for a second VEGF receptor, wherein the **first receptor is KDR and the second receptor is Flt-4**.

III. Claims 4, 19-23, 28, 31, 34, drawn to an antibody having a first antigen binding site specific for a first VEGF receptor and a second antigen binding site specific for a second VEGF receptor, wherein the **first receptor is Flt-1 and the second receptor is Flt-4**.

IV. Claims 36-40, drawn to a **method for making** an antibody having a first antigen binding site comprising a first immunoglobulin heavy chain variable domain and a first immunoglobulin light chain variable domain that specifically binds to an extracellular domain of a first VEGF receptor, and a second antigen binding site comprising a second immunoglobulin heavy chain variable domain and a second immunoglobulin light chain variable domain that specifically binds to an extracellular domain of a second VEGF receptor, wherein the **first receptor is KDR and the second receptor is Flt-1**.

V. Claims 36-40, drawn to a **method for making** an antibody having a first antigen binding site comprising a first immunoglobulin heavy chain variable domain and a first immunoglobulin light chain variable domain that specifically binds to an extracellular domain of a first VEGF receptor, and a second antigen binding site comprising a second immunoglobulin heavy chain variable domain and a second immunoglobulin light chain variable domain that specifically binds to an extracellular domain of a second VEGF receptor, wherein the **first receptor is KDR and the second receptor is Flt-4**.

VI. Claims 36-40, drawn to a **method for making** an antibody having a first antigen binding site comprising a first immunoglobulin heavy chain variable domain and a first immunoglobulin light chain variable domain that specifically binds to an extracellular domain of a first VEGF receptor, and a second antigen binding site comprising a second immunoglobulin heavy chain variable domain and a second immunoglobulin light chain variable domain that specifically binds to an extracellular domain of a second VEGF receptor, wherein the **first receptor is Flt-1 and the second receptor is Flt-4**.

VII. Claims 41-43, drawn to a **method for neutralizing activation** of a first VEGF receptor and a second VEGF receptor in a cell, a method of reducing tumor growth in a mammal in need thereof, and a method for inhibiting angiogenesis in a mammal in need thereof which comprises treating a cell with an antibody having a first antigen binding site specific for the first VEGF receptor and a second binding site specific for the second VEGF receptor in an amount sufficient to neutralize activation of the receptors wherein the **first receptor is KDR and the second receptor is Flt-1**.

VIII. Claims 41-43, drawn to a **method for neutralizing activation** of a first VEGF receptor and a second VEGF receptor in a cell, a method of reducing tumor growth in a mammal in need thereof, and a method for inhibiting angiogenesis in a mammal in need thereof which comprises treating a cell with an antibody having a first antigen binding site specific for the first VEGF receptor and a second binding site specific for the second VEGF receptor in an amount sufficient to neutralize activation of the receptors wherein the **first receptor is KDR and the second receptor is Flt-4**.

IX. Claims 41-43, drawn to a **method for neutralizing activation** of a first VEGF receptor and a second VEGF receptor in a cell, a method of reducing tumor growth in a mammal in need thereof, and a method for inhibiting angiogenesis in a mammal in need thereof which comprises treating a cell with an antibody having a first antigen binding site specific for the first VEGF receptor and a second binding site specific for the second VEGF receptor in an amount sufficient to neutralize activation of the receptors wherein the **first receptor is Flt-1 and the second receptor is Flt-4**.

Linking claims 1-3, 24-27, 30 and 33, will be examined along with Groups I-III if any one of said Groups is elected.

Claims 1-3, 24-27, 30 and 33 link inventions I, II or III. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claims, claims 1-3, 24-27, 30 and 33. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35

U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The Groups of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Group I-III lack unity of invention because the groups do not share same or corresponding technical feature.

Groups I-III lack unity of invention because even though the inventions of these groups require the technical feature of an antibody having a first antigen binding site specific for a first VEGF receptor and a second antigen binding specific for a second VEGF receptor, this technical feature is not a special technical feature as it does not make a contribution over the prior art in view of Lu et al (J Immunological Methods 230: 159-171, 1999; PTO 1449) or Lu et al (Cancer Res 61: 7002-7008, Oct 2001; PTO 1449).

Lu et al (J Immunological Methods 230: 159-171, 1999; PTO 1449) teach an antibody such as diabody having a first antigen binding site such as VH and VL domains of scFv p3S5 or scFv p4G7 antibody specific for a first VEGF receptor such as KDR and second antigen binding site specific for a second VEGF receptor such as VH and VL domains of scFv pDAB24 antibody specific for second VEGF receptor such as Flk-1 (see entire document, page 162, Figures 1A, 2 and 3, Table 1, page 169, col. 1, in particular). The reference further teaches a method of making such antibody (see page 161, construction of the diabody, in particular).

Lu et al (Cancer Res 61: 7002-7008, Oct 2001; PTO 1449) teach an antibody such as diabody having a first antigen binding site such as VH and VL domains of scFv plc11 antibody specific for a first VEGF receptor such as KDR and second antigen binding site specific for a second VEGF receptor such as VH and VL domains of scFv 612 antibody specific for second VEGF receptor such as Flt-1 (see entire document, page 7003, Fig 1, col. 2, in particular). The reference further teaches a method of making such antibody (see page 7003, construction of anti-KDR x anti-Flt-1 Diabody, in particular).

Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention.

Accordingly, Groups I-IX are not so linked as to form a single general inventive concept and restriction is proper.

This application contains claims directed to the following patentably distinct (A) species of antibody that binds to a first receptor KDR comprising the specific combination of six CDRs identifiable in claims 6, 8, 10, 12, 14 and 16 and heavy and light chains identifiable in claims 7, 9, 11, 13, 15, 17 and (B) distinct species of antibody that binds to receptor Flt-1 comprising the specific combination of six CDRs identifiable in claims 19 and 21, and heavy and light chains identifiable in claims 20, 22 and 23, for example.

The species of KDR and Flt-1 antibodies are independent or distinct because claims to the different species recite the mutually exclusive characteristics. For example, these species antibodies have different structure i.e., different CDRs, and different mode of operation, bind to different epitopes on different or the same VEGF receptors. Therefore, they are patentably distinct.

Irrespective of whichever group the applicant may elect, the applicant is further required under 35 U.S.C. 121 to elect (A) a single disclosed combination of six CDR for the heavy and light chain variable domain of a first antigen binding site specific for a first VEGF receptor and (B) a single disclosed combination of six CDR for the heavy and light chain variable domain of a second antigen binding site specific for a second VEGF receptor identifiable in claims 6-17 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 19, 24, 30, 33, 36, 41, 42 and 43 are generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different sequences, classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims

are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9:00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
February 13, 2009